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The Eleventh International Childhood Acute Lymphoblastic Leukemia Workshop Report: Ponte di Legno, Italy, May 6-7, 2009

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Introduction

An international childhood acute lymphoblastic leukemia (ALL) working group was formed during the 27th annual meeting of the International Society of Pediatric Oncology in 1995. Since then, 10 workshops have been held to address many issues that help advancing treatment outcome of childhood ALL but require international collaboration (Table 1). The group was fondly named after "Ponte di Legno", a place in Lombardy, Italy because the first major workshop was held there. In celebration of the 10th anniversary of the first major meeting, the group returned to Ponte di Legno on May 6 and 7, 2009 for its 11th meeting (Fig. 1). During the meeting, Professor Giuseppe Masera was honored for his vision and

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contributions to further develop the International-BFM study group and to co-found the Ponte di Legno working group. The meeting began with the greetings by Professor Andrea Biondi. This report summarizes the data presented and the discussion in the meeting.

Leukemia induction failure

Induction failure due to refractory disease is a rare event in pediatric ALL,1-4 and hence there are only scanty information on this topic in the literature. To identify clinical, biological and prognostic features of these patients, Dr. Martin Schrappe and Dr. Martin Zimmermann analyzed a large cohort of patients enrolled in the clinical trials of 14 cooperative study groups between 1985 and 2000. Induction failure, as defined by the morphological persistence of leukemic blasts in bone marrow (M2 or M3 marrow) or at extramedullary site(s) was found in 1041 (2.3%) of 44,554 patients. Not surprisingly, patients with induction failure were more likely to have adverse risk factors, such as older age, high leukocyte count, T-cell ALL, or the presence of Philadelphia chromosome or 11q23 rearrangements, as compared to the other patients. In spite of the resistance to induction chemotherapy, about one-third of patients were alive at 10 years. Treatment results were particularly poor for patients aged <1 or ≥ 10 years, males, and those with leukocyte count >100 $\times 10^9$/L at diagnosis or large post-induction tumor burden in bone marrow. Additional analyses are underway to determine the heterogeneity in clinical outcome according to genetic features and treatment with or without hematopoietic stem cell transplantation.

Philadelphia chromosome-positive ALL

In a previous retrospective analysis of 326 children with Philadelphia chromosome-positive ALL treated by 10 major study groups between 1986 and 1996, the group showed that there was substantial heterogeneity among this subset of leukemia and that transplantation from matched related donor, but not from unrelated donor, was superior to chemotherapy, in terms of disease-free survival and survival.5 To evaluate the impact of improvements in chemotherapy and stem-cell transplantation, the group performed a second survey of patients treated by 14 major study groups between 1995 and 2005. The study was limited to the 647 patients who had not received imatinib or other tyrosine kinase inhibitors. Preliminary results were presented at the 50th annual meeting of the American Society of Hematology in December 2008. Dr. Maurizio Aricó reported that treatment results of this cohort were significantly better than those of the previous cohorts in terms of complete remission rate (89% vs. 82%), 7-year event-free survival (31% vs. 25%), and 7-year survival (44% vs. 36%). Prognostic factors found in the early study remained important, including age, initial leukocyte count, and early treatment response. Final analysis of outcomes for patients treated with chemotherapy vs. various types of stem-cell transplant is underway. The results will serve as baseline data for future comparison with patients treated with contemporary therapy including the tyrosine kinase inhibitors.

Varicella vaccination for ALL patients

There is some controversy about the potential benefits of varicella vaccination for children with ALL who do not have evidence of prior immunity through natural infection or immunization. The American Academy of Pediatrics has recommended that immunization should be considered for susceptible children with ALL who have been in continuous remission for at least 1 year and have a lymphocyte count greater than 700/μL (0.7×10^9/L) and a platelet count greater than 100×10^3/μL (100×10^9/L) (Red Book, 2006). This recommendation is based on clinical trials that showed vaccination to be safe, immunogenic and effective in leukemic children at risk for serious disease or death.6 In the pivotal trials, maintenance chemotherapy was stopped for one week before and after vaccination, and patients did not receive steroids for one week before and two weeks after vaccination. There are several important factors to be considered when making decisions about varicella immunization of children with ALL. First, the baseline varicella vaccination rates are very different between the United States (high) and Western Europe (relatively low); thus, there may be significant differences in the rates of natural varicella infection and immunity in the community. Second, the risk of serious complications or death from varicella among patients with ALL is poorly defined in the era of effective antiviral therapies. Third, there is concern among some leukemia therapists that stopping continuation therapy for several weeks, at least twice, for vaccination might lead to an increased risk of relapse. Finally, there have been some reported cases of serious complications and death following varicella vaccination.7 These issues prompted the group to review records to determine the incidence of death from varicella in children with ALL. Preliminary review of the data show a death rate of <0.1% from varicella among over 25,000 patients treated by 11 study groups between 1989 and 2008. The death rate was ~0.03% in the United States and ~0.1% in Western Europe, a difference which may reflect a generally higher rate of vaccination for varicella in the general population in the United States. Most of the deaths from varicella occurred in the first year of treatment for ALL. Members of the group do not endorse varicella vaccination in children receiving treatment for ALL because of the potential fatal complication of vaccination, the necessity of withholding chemotherapy that might compromise leukemic control, and the negligible risk of death from varicella infection after the first year of treatment for ALL. Other preventive measures should be considered, such as immunization of household contacts.

Other specific genetic subgroups

Once associated with a poor prognosis, the t(1;19)(q23;p13) with *TCF3-PBX1* (also known as *E2A-PBX1*) fusion has lost prognostic significance, and even become one of the favorable genetic subtypes in some contemporary clinical trials, when treated with intensified chemotherapy.8 Chaired by Dr. Andre Baruchel, the Ponte di Legno group will conduct an inter-group study to confirm his observation that these patients not only have an excellent prognosis, but also rarely have late relapse. In five consecutive FRALLE clinical trials conducted between 1983 and 2009, 140 of 3031 patients (4.6%) have this genotype. The 119 patients who were treated after 1992 in FRALLE 92, 93 and 2000 trials have a significantly better 5-year event-free survival rate than that of 21 patients treated in the earlier clinical trials (86%±4% vs. 52%±11%, P=0.001). Only one of the 119 patients in the recent cohort

relapsed beyond 4 years. Dr. Sima Jeha reviewed the outcome of 41 patients with the t(1;19) treated in 4 consecutive Total Therapy studies between 1991 and 2008 at St. Jude Children's Research Hospital. Their 5-year event-free survival estimate was comparable to that of the other 694 B-cell precursor cases (84.2%±7.1% vs. 84.0%±1.8%, P=0.63).9 All of the relapses among patients with the t(1;19) occurred within four years from diagnosis. Of interest, patients with the t(1;19) had a higher cumulative risk of CNS relapse than the other B-cell precursor ALL cases (9.0%±5.1% vs. 1.0%±0.4%, P<0.001). Dr. Jeha also mentioned that 12 adults with the t(1;19) treated with Hyper-CVAD regimen of the M.D. Anderson Cancer Center also had an excellent 3-year survival rate of 73%.10 Similarly, Dr. Chris Mitchell reported that the 51 patients treated in the MRC study fared as well as those with other B-cell precursor ALL cases (hazard ratio 0.62; 95% confidence interval, 0.28 to 1.39), and only one patient had a late relapse at 4.6 years. Dr. Kjeld Schmiegelow showed that the 47 t(1;19)-positive Nordic patients treated between 1992 and 2007 had a relapse rate of 17.2% with all relapses occurring within 3.5 years from diagnosis, and the relapse risk was not related to gender, era of therapy (NOPHO ALL-92 vs ALL-2000 protocols), or the leukocyte count at diagnosis (10 of 11 patients with a leukocyte count above 40×10^9/L were in first remission). With the exception of 67 patients treated in the CCG 1800 series (1989 to 1995) who had a 5-year event-free survival of 68.6%±5.8%, Dr. Stephen Hunger reported that patients with the t(1;19) fared as well as the other B-cell precursor ALL cases treated in the CCG 1900 series (1996 to 2002) and the POG studies (1986 to 1999). Hence, there appears a consensus that t(1;19) cases fared as well as those with other B-cell precursor ALL, and that late relapse is exceptional among patients with this genotype. Dr. Hunger will chair a Ponte di legno inter-group study to evaluate cases with the t(17;19)(q22;p13)[*TCF3-HLF* fusion], a rare subset of ALL often associated with hypercalcemia and a dismal prognosis.11

Since its first description as a non-random chromosomal abnormality in B-cell precursor ALL in the mid 1990s, 71 cases with the dic(9;20)(p13;q11) have been reported.12,13 Approximately, 90% of the cases were children or adolescents, together accounting for 2% of childhood B-cell precursor ALL. Because the prognostic significance of this group is unknown, participants in the Ponte di Lengo workshop held in Atlanta in December 2007 decided to initiate a retrospective analysis of patients with this genotype. In this meeting, Dr. Kjeld Schmiegelow summarized the published review by Dr. Erik Forestier on 71 dic(9;20)-positive cases including 24 patients from the NOPHO group.12 These patients have female predominance (1.7 fold), an age incidence peak at 3 years, a relatively high presenting leukocyte count (median, 24×10^9/L), and a relatively high frequency of CNS involvement (10%). While the event-free survival of the NOPHO cohort was 67%, Dr. Schmiegelow emphasized that all relapses occurred within 3 years from diagnosis, the salvage rate was above 50%, and the *in vitro* drug sensitivity is significantly higher for asparaginase, cytarabine, and corticosteroids than that of other B-cell precursor ALL.13 Dr. Oskar Haas described the 20 patients enrolled in the BFM 2000 study. These patients also had female predominance (80%), a median age of 3.9 years, a relatively high presenting leukocyte count (median, 31.5×10^9/L), and a high frequency of CNS involvement (20%). The 5-year event-free survival was 81%±10%, a result which appeared superior to that of the 24 patients treated in the NOPHO study. Dr. Haas attributed the seemingly better outcome to the more

intensive remission induction and early re-intensification treatment, especially with the use of asparaginase in the BFM 2000 protocol. Dr. Christine Harrison confirmed the female predominance (63%) and a median age of 3 years among 51 patients treated in the UK series; there was no difference in treatment outcome between patients with or without dic(9;20) treated in MRC ALL97 study, but all relapses occurred within approximately 3 years from diagnosis. A larger study of dic(9;20) cases drawn from the Ponte di Legno group will be performed by Dr. Forestier.

Approximately 3% of childhood B-cell precursor ALLs harbour an intrachomosomal amplification of chromosome 21 (iAMP21), first detected by FISH using the *ETV6-RUNX1* (also known as *TEL-AML1*) probe. These cases have been associated with an older children and a lower white blood cell count,14,15 and a poor prognosis in two recent small series. 16,17 The current definition of iAMP21 relies on demonstration of the combination of 5 or more *RUNX1* signals using FISH probes directed to *RUNX1*, and the absence of other established chromosomal abnormalities (e.g. hyperdiploidy and *ETV6-RUNX1* fusion). Loss of one copy of chromosome 21 in association with an abnormal [der(21)] or an unidentified marker chromosome is highly suggestive of iAMP21 which must be confirmed by FISH. The common amplified region on 21q is around 6.5 Mb and includes approximately 60 genes.18 The group has undergone a retrospective study of such cases, led by Drs Harrison and Haas. More than 300 such cases will be reported in the final analysis which will improve characterization of the abnormality itself as well as the presenting features and clinical outcome of the patients.

The prognosis of the CD10-negative ALL in children over one year of age is unclear. This heterogeneous group of cases represents 3% of childhood B-cell precursor ALL cases and comprises *MLL*-rearranged (approximately two third of the cases) and *MLL* non-rearranged cases, according to Dr.Anja Moericke of the BFM group. The overall 10 year event-free survival of the 228 cases treated in the BFM protocols between 1986 and 2006 was 62 ± 3 %, a result clearly inferior to that of the CD10-positive cases. Because the rare subgroup without *MLL* rearrangement is still poorly characterized, the group has thus decided to launch a retrospective study on all CD10-negative B-lineage ALL cases treated by the participating groups between 1995 and 2005.

Down Syndrome and ALL

Children with Down syndrome (DS) have a 10- to 20-fold increased risk of developing acute leukaemia, either ALL or acute myeloid leukaemia. Mutations in the transcription factor GATA1 have been implicated in pathogenesis of DS patients with acute myeloid leukemia. 19 Dr. Shai Izraeli reviewed the recently described mutations in the Janus kinase 2 gene (JAK2) found in 18% of DS ALL cases, mainly occurring at a specific site, arginine 683 (R683).20-23 Reported cases include also two DS ALL cases with complex in-frame insertion and deletion events proximal to R68321 and one case with a 5-amino acid deletion including R683;20 the majority cases had R683 point mutations.21,22 These mutations cause JAK2 constitutive activation and are associated with cytokine-independent growth in vitro.21,22 Altogether, 42 cases (19%) with JAK2 mutations have been identified among a cohort of 242 children with ALL and DS.21-24 Dr. William Carroll remarked that the same

frequency has also been found in the Children's Oncology Group DS ALL project (11 mutations of JAK2 (R683) in 59 samples). The correlations of *JAK2* mutations and the presenting features or clinical outcome have yet to be defined. In this regard, in a recent study of children without DS, mutations of JAK (JAK1, JAK2, JAK3) were found in approximately 10% of *BCR-ABL*-negative high-risk B-cell precursor ALL cases.25 The types of mutation found in the JAK2 gene (mainly R683) do not overlap with that found in myeloproliferative diseases (V617F). According to Drs Izraeli and Carroll, gene expression profile studies and DNA copy number variation studies suggest that DS ALL is an heterogeneous disease which does not fall in the same clusters with those with *ETV6-RUNX1*, *TCF3-PBX1*, or hyperdiploid ALL.

Dr. James Whitlock described high mortality rates in children with DS ALL treated in the COG studies AALL0331 (3-drug induction, 11.5%) and AALL0332 (4-drug induction, 15%) which were attributed to the use of dexamethasone. Two main modifications were successful in reducing the rate of mortality in the AALL0331 study: the interrupted administration of dexamethasone during remission induction and the addition of leucovorin rescue after intrathecal injection of methotrexate. However, substitution of dexamethasone by prednisone during the 4-drug induction of AALL0332 did not result in the same gain and the study has been closed. Despite the fact that children with ALL and DS in all study groups experienced more adverse event that non DS patients, a review of the protocols from cooperative groups has revealed a marked heterogeneity in terms of the nature of glucocorticoid treatment, three or four-drug induction, leucovorin rescue after intrathecal treatment, the use of high-dose methotrexate and of central-nervous-system irradiation. There was a discussion on whether or not new drugs targeting JAK2, such as XL-019 (Exelixis), TG101348 (Targegen), INCB018424 (Incyte), CEP-701/lestaurtinib (Cephalon) used in clinical trials for adults with myeloproliferative syndrome, should be tested in this population with increased toxicity to conventional multi-agent chemotherapy.

An international retrospective study under the auspices of the group has already been launched to define clinical and biologic features and treatment outcome of DS patients with ALL treated in prospective trials between 1995 and 2005. The study will also focus on the analysis of toxic deaths during remission induction and postremission therapy and their relationship with specific treatments blocks and length of therapy.

Results of ALL treatment: New endpoints needed?

Dr. Paul Gaynon, Dr. Maria Grazia Valsecchi, and Dr. Anja Möricke discussed a very complex issue which has gained more interest in the recent years when cure rates in pediatric ALL approached 90%. From a methodological point of view, endpoints for clinical interventions should be relevant, quantifiable, objective, sensitive, and specific. The question if new study endpoints are needed was derived from the observation that recurrence of disease has become so rare (at least in some subsets) that other events such as death in induction, death in remission, and second malignancies have become important competing events. Thus, overall survival could be considered the most relevant endpoint when comparing randomized interventions. However, most clinical trials are designed and powered to address questions with event-free or disease-free survival as major endpoints.

There was an agreement that any early fatal event (death in induction or on therapy in remission) is more relevant to determine the quality of a given treatment strategy than the death due to disease after a (late) recurrence. There was a consensus that although event-free survival or overall survival probabilities are key endpoints for clinical trials, other indicators of treatment quality should not be missed. Treatments can be compared on the basis of toxicity parameters, e.g. those defined by NCI toxicity scores, or by the incidence of (severe) adverse events. It appears, however, that the standard scores may miss some of the relevant toxicities. Therefore, treatment burden may be assessed more adequately by recording not only death in induction or in remission but also the near misses together with the use of pressors and ventilation. In addition, a standardized reporting of (unexpected) hospitalization; prolongation of treatment phase (in days) beyond that defined in the protocol; number and duration of interventions such as transfusions, intravenous narcotics, antibiotics or antifungal agents, parenteral nutrition,: and the incidence of forced treatment change (omission or reduction of prescribed antileukemic drugs) has been proposed.

For ALL, complete assessment of sentinel events should include not only the acute and intermediate adverse events such as cerebral thrombosis or hemorrhage, seizures, pancreatitis, veno-occlusive disease, and osteonecrosis (symptomatic vs asymptomatic), but also the late complications (e.g., second neoplams and cardiac failure) which require long-term follow-up to assess. Dr. Gaynon pointed out that the accurate assessment of the late events could be difficult in the large cooperative group studies.

Second neoplasm will develop in 1-2% of ALL survivors within 5-10 years. The cumulative rate may reach 30% or more depending on duration of follow-up, inclusion of benign tumors, treatment modalities and monitoring (e.g. meningiomas after radiotherapy). It is well known that secondary myeloid malignancies develop early (generally within 5 years) while carcinomas and meningiomas occur late (beyond 20 years or more). There is now evidence that the intensity of mercaptopurine treatment and thiopurine methyltransferase genotype or activity play an important role in the development of secondary myeloid malignancies.26 The group has agreed to conduct a retrospective analysis, led by Dr. Kjeld Schmiegelow and Dr. Maria Grazia Valsecchi on individual data of cases with major subtypes of second malignant neoplasm to better define the risk features (lineage, karyotype, therapy), the epidemiology, the time of occurrence and subsequent survival.

Early treatment response as measured by the use of sensitive techniques to detect minimal residual disease (MRD)27-29 has been proposed to serve as a new endpoint to evaluate treatment interventions. Dr. Valsecchi pointed out that a new drug or regimen may demonstrate better activity in the MRD assay than the control strategy but could still produce the same overall event-free survival or overall survival if the new treatment does not yield more effective long-term result than the control regimen. Obviously, feasibility and reproducibility of MRD assessment have to be proven for each specific ALL subgroup and for each method.

How to translate pharmacogenetic data into systematic use in clinical studies

Dr. Mary Relling and Dr. William Evans reviewed recent results which had demonstrated clinical relevance of pharmacogenetic and pharmacodyamic studies in pediatric ALL.30-32 High-throughput genome-wide analyses have revealed a number of genes which may be quite clinically relevant depending on the composition of therapy. They presented proposed procedures being developed at St. Jude Children's Research Hospital to offer genotyping for a growing list of genetic tests (including *TPMT, CYP2D6, UGT1A1, CYP2C9, VKORC1, CYP2C19*) offered with CLIA (Clinical Laboratory Improvement Amendments) certification that can be posted in medical records. The greatest clinical benefit relevant for patients with ALL is likely for *TPMT* and *CYP2D6*.33,34 In future studies, aims will include establishing procedures by which genomic results can move from research into clinical settings for pre-emptive use, particularly if high-throughput technology allows faster and more comprehensive individual screening of germline genomic variation.

Molecularly target therapy

Dr. Stephen Hunger highlighted that event-free survival and overall survival rates have improved for almost all subsets of ALL over the last two decades in the Children's Oncology Group. Further improvement in cure rates may require more specifically targeted therapy similar to the tyrosine kinase inhibitor therapy that has recently been implemented for Philadelphia chromosome-positive ALL. In a recent study, Children's Oncology Group evaluated whether imatinib (340 mg/m^2 per day) together with an intensive chemotherapy regimen would improve outcome of this subset of patients.35 Exposure to imatinib was increased progressive in 5 patient cohorts, from 42 in the first cohort (7 patients) to 280 continuous days in the last cohort (cohort 5, 50 patients), prior to continuation therapy. Continuous imatinib treatment significantly improved outcome of patients in the cohort 5 with 3-year event-free survival rate of 80%±11%, more than twice of that (35%±4%) for historical controls. The three-year results were similar for patients in the cohort 5 treated with chemotherapy (88%±10%) or matched-sibling donor transplant (57%±22%). Thus far, no relapses have occurred in patients who have completed treatment with chemotherapy plus imatinib. There were no significant toxicities with the added imatinib to the treatment. Children's Oncology Group will be exploring Dasatinib during both induction and post-induction therapy (AALL0622 study), due to its potential advantages compared to imatinib, including higher efficacy towards tyrosine kinase mutants.

The group collaboration and data-sharing have made major contributions, with important articles published in high-impact journals describing rare subsets of childhood ALL. Although this activity will continue, the participating groups agreed that the time has come to move forward and collaborate on phase III trials to explore the best therapy for rare ALL subsets. For Philadelphia-chromosome ALL, these studies could explore the necessity for intensive chemotherapy, when continuous, intensive tyrosine kinase inhibitor is given; the most effective chemotherapeutic backbone to tyrosine kinase inhibitor therapy; the most effective inhibitor (e.g. imatinib vs danatinib or nilotinib); and the potential indications for transplantation (e.g. those with high post-induction minimal residual disease).

Other subsets of ALL could similarly benefit from international collaborative trials. Dr. Hunger suggested that it is logical to test JAK inhibitors combined with intensive chemotherapy for ALL patients with mutations that affect the JAK pathway (e.g. JAK1, JAK2, JAK3). Mullighan and associates reported recently that JAK mutations occur in children (lacking Down Syndrome) with B-cell precursor ALL.36 These mutations, which appear to be at least as common as Philadelphia chromosome-positive ALL, are associated with other high risk features including IKAROS deletions and an activated kinase or BCR/ABL1-like gene expression profile,37,[38] and a poor outcome. In vitro studies show that JAK mutations confer growth factor independence, which can be overcome with targeted agents.

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Fig. 1.
Participants of the Eleventh International Workshop in Ponte di Legno (Italy).

Table 1

Ongoing Ponte di Legno Inter-group Studies in Childhood Acute Lymphoblastic leukemia

Project	Principal Investigator
Long-term follow-up of Clinical Trials Common presentation of data	Individual group chairs
Down syndrome ALL Clinical features and outcome	Trudy Buitenkamp, Michael Zwaan, Shai Izraeli
Philadelphia chromosome-positive ALL Clinical features and outcome	Maurizio Aricó
t(1;19)(q23;p13) Clinical features and outcome	Andre Baruchel
t(17;19)(q22;p13) Clinical features and outcome	Stephen Hunger
dic(9;20)(p13;11) Clinical features and outcome	Erik Forestier
***AML1*-amplification** Clinical features and outcome	Christine Harrison
t(4;11)(q21;q23)/CD10-negative ALL Clinical features and outcome	Jim Nachman, Anja Möricke
Induction failure Clinical features and outcome	Martin Schrappe
Varicella vaccination	Miguela Caniza, Giuseppe Masera
Second malignant neoplasms Risk factors and outcome	Kjeld Schmiegelow, Maria Valsecchi